COLOBOMATOUS MALFORMATIONS OF THE EYE*

BY *Irene H. Maumenee,* MD AND (BY INVITATION)
Thomas N. Mitchell

INTRODUCTION

AT BIRTH OF A CHILD WITH COLOBOMATOUS MALFORMATIONS OF ONE OR both eyes questions regarding visual prognosis, possible systemic complications, and recurrence risks will arise. Multiple reviews of the variable phenotypes of colobomatous malformations of the eye have been written, but none addresses the specific risk of extraocular malformations nor the recurrence risk for subsequent children or of offspring of an affected individual.[1-22]

METHODS

With the above questions in mind, we reviewed the data on 82 patients from 70 families examined at the Johns Hopkins Center for Hereditary Eye Diseases between 1972 and 1989. A colobomatous malformation was defined as any fusional abnormality of the fetal fissure, including isolated iris coloboma and isolated coloboma of the optic nerve head, but excluding pits of the optic nerve head, isolated morning glory disc, and nanophthalmos. Such exclusion is obviously arbitrary, especially since severe microphthalmos and anophthalmos were included, even though no coloboma was identified. All patients had complete eye examinations, a medical history, and a physical examination were obtained. A chromosomal analysis was only performed in the presence of mental retardation. The family was advised about the possibility of delayed onset growth hormone

*From the Johns Hopkins Center for Hereditary Eye Diseases of the Wilmer Ophthalmological Institute, The Johns Hopkins Medical Institutions, Baltimore, Maryland. Supported in part by the Krieble and Walter Edel Funds of the Johns Hopkins Center for Hereditary Eye Diseases.

deficiency, but neural imaging was only obtained in the presence of neurologic signs. Renal ultrasounds were deferred except if genital anomalies were present. All patients were personally examined except for the reportedly affected deceased older sib of one of our probands. The child died from renal failure. He had mental retardation and hepatomegaly. A great effort was made to examine both parents of all patients for disc anomalies and peripheral colobomas, a lesser effort was made to examine ostensibly normal sibs, unless genetic counselling for their prospective offspring was requested.

The segregation parameters were estimated using the Weinberg correction as well as computerized segregation analysis programs.

RESULTS

Our sample of 82 patients included 36 females and 45 males, in one case the sex was not recorded. Two children with an XY chromosome constitution are raised as females because of ambiguous genitalia. They are counted as male in this classification.

The age range of the patient population was from neonate to 59 years with a median of 11.5 years; 14 patients were 31 years or older and presumed to have completed their families.

The visual acuity could be assessed in 64 patients; it could not be adequately measured in 18 because of either young age or mental retardation (Table I).

Associated ocular malformations are summarized in Table II. Acquired retinal detachment was seen in one eye of one patient and both eyes of another patient. A posterior staphyloma was seen in all affected members

TABLE I: VISUAL ACUITY

21	Patients had 20/40 or better in better eye
10	Patients had 20/50 to 20/100 in better eye
2	Patients had 20/200 to 20/400 in better eye
16	Patients had fixate & follow in better eye
8	Patients had LP or LP with projection in better eye
7	Patients had NLP in both eyes
64	Better eyes

LP, light perception; NLP, no light perception.

TABLE II: OCULAR COMPLICATIONS

	EYES
Aniridia	1
Congenital cataract	6
Glaucoma, congenital	1
Lens coloboma	1
Megalocornea	1
Microcornea	6
High myopia	5
Peters anomaly	2
Ptosis	2
Marcus Gunn jaw winking syndrome	1
Retinal detachment	3
Staphyloma, posterior	4

of one family with autosomal dominant colobomatous microcornea and macrophthalmia.[23] Presenile cataracts were also common.

Systemic complications are summarized in Table III. Midline defects such as clefting, cardiovascular or urogenital anomalies were frequent as were intracranial malformations. Of special interest is the large number of digital anomalies.

There were 28 cases of identifiable syndromes. Five patients had a chromosomal abnormality; two cases of 4p- (Wolf-Hirschorn syndrome), two cases of trisomy 13, and one patient with an XXXY chromosomal constellation. These were all isolated cases and they were excluded from the segregation analysis, which tests for probabilities of mendelian versus polygenic inheritance patterns and versus environmental factors. One

TABLE III: CLINICAL DATA — OUT OF 82 PATIENTS

Systemic complications:		
There were 29 incidences of "midline" defects, occurring in 22 patients		
8 Clefting		
8 Cardiovascular		
7 Urogenital (4 kidney, 3 genitalia)		
3 Intracranial (including Dandy-Walker cyst)		
3 Hydrocephaly		
Mental retardation	12 (+8?)	(?= unsure if existing)
Deafness	17 (+1?)	
Digital	11	
Short stature	05 (+3?)	

patient with Lenz microphthalmia syndrome and one with the Ito syndrome were similarly excluded, because inheritance patterns are well identified for these two syndromes. All other patients including those with CHARGE association, were included.

There were eight pedigrees permitting identification of a likely mode of inheritance: five pedigrees were diagnostic of or best compatible with autosomal dominant inheritance; there were three pedigrees of likely autosomal recessive inheritance, with two affected sibs and normal parents in two instances, and one instance of a singly affected offspring of a first cousin marriage. One pedigree (Fig 1) consisted of a total of six sibs, three affected brothers, one normal male, and two normal female sibs. A total of six offspring are alive and well in the subsequent generation. The parents have been evaluated and have no evidence for a colobomatous lesion. Summing over this heterogeneous sample, segregation analysis did not give a fit with any specified model. An empirical risk factor of 9% was calculated for a subsequent child, and of 46% for the offspring of an affected person.

DISCUSSION

Colobomatous malformations of the eye affect 5% to 10% of blind children in Europe[24] and is found in 2% of blind adults.[25] Frequencies in neonates are similar.[26] But not all patients with such a malformation complex are blind, the visual acuity among our patient population was 20/40 or better

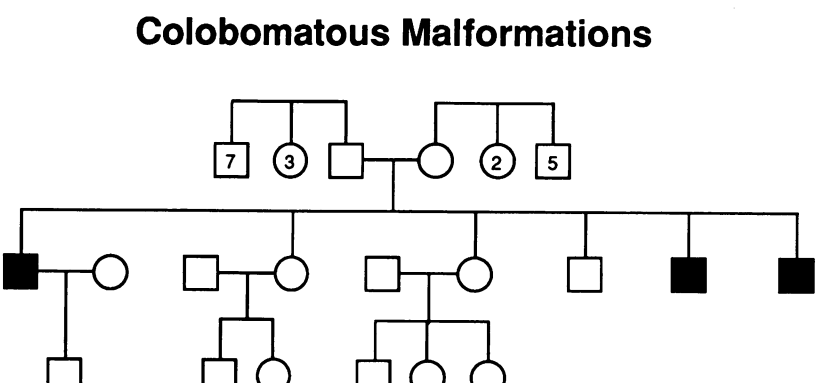


FIGURE 1
Pedigree of family with colobomatous malformations in three male sibs. The pedigree pattern is compatible with either X-linked or recessive inheritance.

in the better eye in one-third of the patients. No prognosis could be made about the visual acuity from appearance of the fundus at birth. Good visual acuity could be observed in severely malformed globes, and poor visual acuity in mild optic nerve hypoplasia, when unilateral.

There was a high degree of variability of ocular malformations between the two eyes of one patient and among family members. The associated ocular malformations varied from Peters anomaly, lens dislocation, and congenital cataracts to severe microphthalmia. High myopia was seen in five patients; colobomatous lesions do not necessarily entail a small globe or hypermetropia. A unilateral morning glory disc was seen in the otherwise normal mother of a girl with CHARGE association. Morning glory disc should be considered a colobomatous malformation, as should be hypoplastic optic discs, since we also observed the combination of unilateral hypoplastic optic nerve in a father and bilateral colobomatous malformation with unilateral microphthalmia in the daughter (Fig 2).

Evidence for neural tube defects varied from hydranencephaly over spina bifida to Dandy-Walker cyst. Midline defects were very common and are probably underestimated since a diagnostic work-up was only done when the patient was symptomatic. The most common clinical diagnosis was the CHARGE association, a diagnosis made when four out of its six signs were present in a given patient, the six signs being coloboma, heart disease, choanal atresia, growth and mental retardation, genitourinary and ear abnormalities, either in the form of deafness or external ear deformities.[10] A large number of our patients qualified for this diagnosis, which in the absence of a molecular marker remains imprecise.

Recurrence figures were estimated for the subsequent child of healthy unrelated parents as 9%, and for the children of an affected person as 46%. If a clearcut pedigree pattern is observed this overrides above risk estimates. These estimates are based on small sample sizes, since our data are heavily weighted towards the young age. Only 14 patients are older than 30 years, and could be assumed to have completed their family. Fifty-three patients were singly affected and either an only child or the last of a sibship. Thus fertility was reduced. These risk estimates are meant to serve as guidelines in the absence of a positive family history. Every effort should be made to examine both parents of such patients for minor manifestations of the gene, such as a small coloboma in the inferior retinal periphery or an anomalous disc. In such a case the recurrence risk for a subsequent child rises from 9% towards 50%, though not reaching it. The recurrence risk after birth of an affected child is simply never zero and familial cases of complex malformation syndromes were seen as well as intrafamilial variability of severity of the disease complex and of the

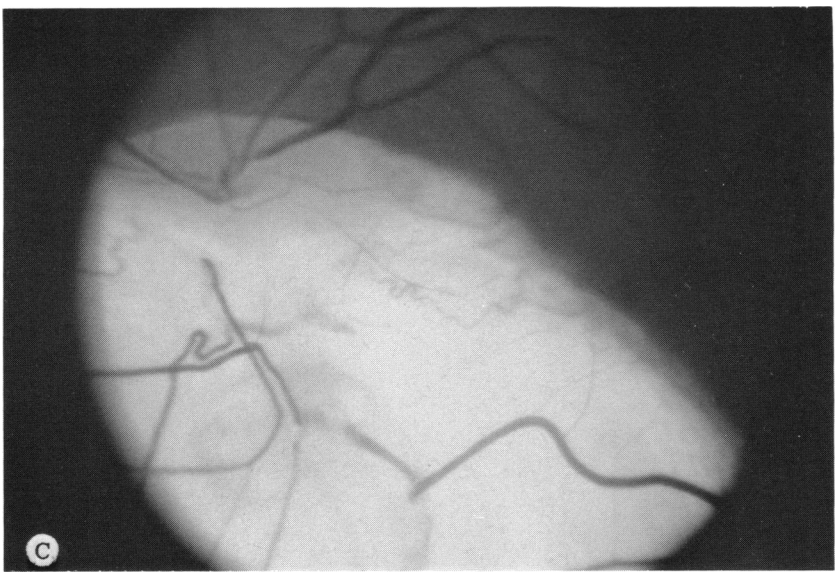
ocular malformation.

No single gene for colobomatous malformations has been identified to date and this search will be difficult given the absence of large pedigrees and the unlikely significance of chromosomal aberrations as pointers for search for a gene.[27] As molecular bases for Mendelian diseases are discovered and their pathogeneses elucidated, dysembryology remains a major frontier. Definition of molecular defects of colobomatous malformations may have to await the results of the proposed Human Genome Project (HUGO).

Opitz defined "developmental fields" as body parts which can be affected in an identical manner by different insults.[28-30] Limbs are obvious such fields and can be identically affected by environmental and genetic factors (phocomelia). The eye should be defined as a "developmental field." The midline is similarly proposed as a developmental field,[28] based on the observation of nonrandomness of occurrence of midline malformation syndromes. We observed digital malformations in 11 patients with coloboma, even though limbs are recognized as developmental fields sui generis. Based on the clinical variation observed in pedigrees, we propose that single gene defects exist, which act in the early stages of the developing embryo prior to definition of "limb," "midline," and "ocular" fields. The Lenz microphthalmia syndrome,[31] which combines coloboma, mental retardation, digital and urogenital anomalies, is transmitted through an X-linked gene, and should serve as example of such a mechanism. We moreover propose that the "limb fields" separate before the ocular fields from the "midline" field, since we did not see a single instance of combined ocular and limb anomalies without midline defects, but many instances of combined ocular and midline defects without limb anomalies. This mechanism would exist in addition to the likely existence of pathogens which will affect different tissues which are simultaneously undergoing their sensitive developmental period.[32]

Abnormalities of virtually every chromosome have been identified in patients with colobomatous malformations. Pedigrees with autosomal dominant, recessive, and X-linked inheritance have been described, dilantin ingestion has been incriminated. The abnormalities vary from complex malformation syndromes, often referred to as CHARGE association, if the chromosome are normal, to minor ocular abnormalities such as an iris coloboma. These various phenotypes may be seen in the same family, and significant differences are often seen in the two eyes of one patient (Fig 2). However, under the assumption of a single gene defect a similar phenotype is expected for sibs and certainly for the two eyes of one individual. The following mechanism is proposed to explain the

FIGURE 2
A-C: Clinical appearance of patient with colobomatous microphthalmia; note corneal asymmetry and fundus findings. D & E: Hypoplastic left optic nerve in patient's father.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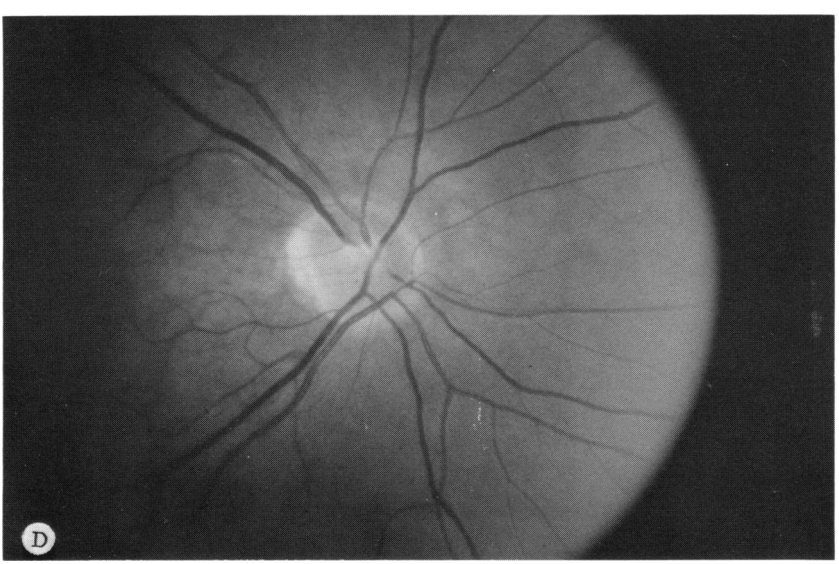
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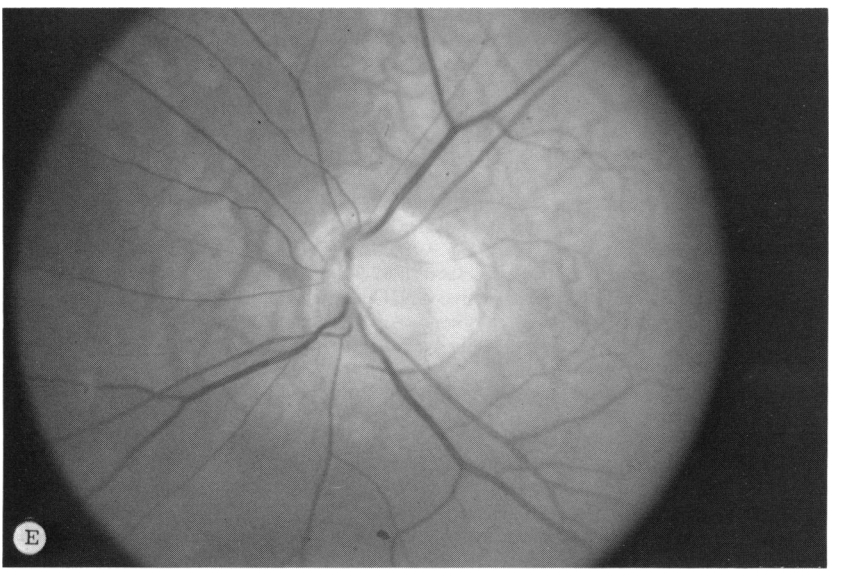

variable expressivity. Insults involving multiple organs have to occur at an early embryologic stage, at a time when the phylogenetic determination has been made but the phylogenetic potential is still large, that is when plasticity still exists. Repair, though imperfect, could occur through pluripotent cells. Such repair has been demonstrated in the newt through the ingenious experiments of Spemann,[33,34] and may account for the clinical variability seen as consequence of a single gene defect. Laboratory animal experimentation will give answers, which otherwise will have to await elucidations expected from HUGO.

REFERENCES

1. Apple DJ, Rabb MF, Walsh PM: Congenital anomalies of the optic disc. *Surv Ophthalmol* 1982; 27:3-41.
2. Brown GC, Augsburger JJ: Congenital pits of the optic nerve head and retinochoroidal colobomas. *Can J Ophthalmol* 1980; 15:144-146.
3. Brown GC: Optic nerve hypoplasia and colobomatous defects. *J Pediatr Ophthalmol Strabismus* 1982; 19:90-93.
4. Duvall J, Miller SL, Cheatle E, et al: Histopathologic study of ocular changes in a syndrome of multiple congenital anomalies. *Am J Ophthalmol* 1987; 103:701-705.
5. Gardner TW, Zaparackas ZG, Naidich TP: Congential optic nerve colobomas—CT demonstration. *J Comput Assist Tomogr* 1984; 8:95-102.
6. Kremer I, Cohen S, Bar Izhak R, et al: An unusual case of congenital unilateral Coats' disease associated with morning glory optic disc anomaly. *Br J Ophthalmol* 1985; 69:32-37.

7. Lin CCL, Tso MOM, Vygantas CM: Coloboma of optic nerve associated with serous maculopathy. *Arch Ophthalmol* 1984; 102:1651-1654.
8. Mafee MF, Jampol LM, Langer BG, et al: Computed tomography of optic nerve colobomas, morning glory anomaly, and colobomatous cyst. *Radiol Clin North Am* 1987; 25:693-699.
9. Orcutt JC, Bunt AH: Anomalous optic discs in a patient with a Dandy-Walker cyst. *J Clin Neuro-Ophthalmol* 1982; 2:43-47.
10. Pagon RA: Ocular coloboma. *Surv Ophthalmol* 1981; 25:223-236.
11. Pisteljic DT, Vranjesevic D, Apostolski S, et al: Poland syndrome associated with morning glory syndrome (coloboma of the optic disc). *J Med Genet* 1986; 23:364-366.
12. Ribeiro-da-Silva J, Castanheira-Dinis A, Agoas V, et al: Congenital optic disc deformities. *Ophthalmic Pediatr Genet* 1985; 5:67-70.
13. Rosenberg LF, Burde RM: Progressive visual loss caused by an arachnoidal brain cyst in a patient with an optic nerve coloboma. *Am J Ophthalmol* 1988; 106:322-325.
14. Savell J, Cook JR: Optic nerve colobomas of autosomal-dominant heredity. *Arch Ophthalmol* 1976; 94:395-400.
15. Taylor DSI: The genetic implications of optic disc anomalies. *Trans Ophthalmol Soc UK* 1985; 104:853-856.
16. Van Dalen JTW, Delleman JW, Yogiantoro M: A discussion of 61 cases of optic nerve coloboma. *Doc Ophthalmol* 1983; 56:177-181.
17. Weaver RG, Cashwell LF, Lorentz W, et al: Optic nerve coloboma associated with renal disease. *Am J Med Genet* 1988; 29:597-605.
18. François J: Hérédité des affections colobomateuses du globe oculaire. *Ann D'Oculist* (Paris) 1966; 199:545-573.
19. Warburg M: Genetics of microphthalmos. *Int Ophthalmol* 1981; 4:45-65.
20. ———: Microphthalmos and colobomata among mentally retarded individuals. *Acta Ophthalmol* 1981; 59:665-673.
21. François J: Colobomatous malformations of the ocular globe. *Int Ophthalmol Clin* 1968; 8:7979-816.
22. Hussels IH: Midface syndrome with iridochoroidal coloboma and deafness in a mother—Microphthalmia in her son. *Birth Defects: Original Article Series* 1971; 7:269.
23. Bateman JB, Maumenee IH: Colobomatous macrophthalmia with microcornea. *Ophthalmic Pediatr Genet* 1984; 4:59-66.
24. Schappert-Kimmijser J: Causes of severe visual impairment in children and their prevention—The Committee for Special Study of Severe Visual Impairment in Children of the International Association for the Prevention of Blindness. *Doc Ophthalmol* 1975; 39:213-364.
25. Lindstedt E: Congenital malformations of the eye. *Acta Ophthalmol* (Kbh) 1968; 46:355-359.
26. Goravalingappa JP, Nashi HK: Congenital malformations in a study of 2398 consecutive births. *Indian J Med Res* 1979; 69:140-146.
27. Warburg M, Friedrich U: Coloboma and microphthalmos in chromosomal aberrations. *Ophthalmic Paediatr Genet* 1987; 8:105-118.
28. Opitz JM, Gilbert EF: CNS anomalies and the midline as a "developmental field." *Am J Med Genet* 1982; 14:443-455.
29. Opitz JM: The developmental field concept. *Am J Med Genet* 1985; 21:1-11.
30. ———: The developmental field concept in clinical genetics. *J Pediatr* 1982; 101:805-809.
31. Traboulsi EI, Lenz W, Gonzales-Ramos M, et al: The Lenz microphthalmia syndrome. *Am J Ophthalmol* 1988; 105:40-45.
32. Moore KL: *The Developing Human: Clinically Oriented Embryology*. Philadelphia, WB Saunders, 1982.
33. Spemann H, Mangold H: Über Induktion von Embryonalanlagen durch Implantation artfremder Organisatoren. *Arch Mikrosk Anat* 1924; 100:599-638.
34. Spemann H: *Embryonic Development and Induction*. New Haven, Yale University Press, 1938. (Reprinted New York, Hafner Publishing Co, 1962.)

DISCUSSION

DR RICHARD M. ROBB. Doctors Maumenee and Mitchell have set for themselves a difficult task in reviewing their patients with colobomatous malformations of the eye. They propose to address questions such as; "What is my child going to see?", "Are there other associated problems?", "Why did this happen to my child and might it happen to other children in the future?" The answers to these questions remain elusive, even after this careful clinical review. The problem is that colobomas of the eye are not caused by one genetic or developmental mechanism, and most colobomas are not in themselves characteristic of a specific entity. One is therefore dealing with a mixed group of patients and must be alert for other clues to the underlying cause.

Probably the most interesting data from this review of 82 patients is the list of associated systemic anomalies. Midline defects of various organs occurred in 27% of patients. Deafness occurred in 20%, digital anomalies in 13%, and mental retardation in something between 15% and 24%. These data suggest what sort of associated problems to look for. In addition, 28 patients had identifiable syndromes, most of them uncommon if not rare. The CHARGE association of anomalies occurred in six patients, but this is not likely to be overlooked when it includes congenital choanal atresia. Excluding these syndromes, which were all sporadic in their occurrence, an empirical risk factor of 9% was found for subsequent siblings. This would, of course, be too high for some families and too low for others.

This series of patients, coming from a major referral center, probably includes more of these syndromes and associated anomalies than might be seen in other settings. Nevertheless it is useful to know what sorts of other problems may occur in association with colobomas of the eye and something about the possibilities of genetic transmission. One's predictive batting average may not be much better than most real baseball players achieve, but it is nice to know that you are at least in the right ball park. I want to thank Doctor Maumenee for letting me look at a preliminary form of the manuscript and the Society for the opportunity to discuss this paper.

DR ROBERT C. DREWS. I want to make two points. First of all, it was overwhelming to see these statistics. They are very different from what we see in a general ophthalmological practice where coloboma of the iris, choroid or optic nerve is not that unusual, and where the vast majority of these patients are perfectly normal in all other respects. Secondly, when you talk about visual prognosis, there are a small subgroup of these patients with coloboma of the iris or optic nerve who have heterochromia. The eye with the coloboma will be the darker eye and that eye usually has a refractive amblyopia secondary to a high oblique astigmatism.

DR MARSHALL M. PARKS. Your presentation emphasized the genetic embryogenesis and associated systemic anomalies of colobomatous malformations of the eye. However, I would like to learn from your extensive experience about the frequen-

cy of the development of serous retinal detachment in this disorder. You did list retinal detachment as a complication on one slide but you made no comment about it in the oral part of your presentation. My interest in this complication comes from my experience of the following three patients with a colobomatous malformation of the eye that initially had a flat retina but now the eye is blind due to irrepairable retinal detachment. Moreover, I find that our postresidency fellows in pediatric ophthalmology were not prepared during their residency training programs to be aware of the potential for development of this complication in the eyes with colobomatous malformations. Do you have any facts on the frequency of serous detachment of the retina developing in this malformation and what is your recommendation on the need for follow-up observation of these patients in order to detect the detachment before it becomes irrepairable?

Dr R. Linsy Farris. I would just like to reinforce Doctor Maumenee's comment about treating the amblyopia in these patients. Considerable effort on the part of the ophthalmologist and family is required to fit and maintain a contact lens on these small eyes. But not to be overlooked is the additional extra effort that is required to maintain treatment of the associated amblyopia. Surprising visual results can be obtained in these small eyes with attention to amblyopia and contact lens fitting by the ophthalmologist.

Dr Thomas O. Wood. As opposed to fitting these patients with contact lenses have you tried epikeratophakia? In our limited experience, our most satisfactory results with epikeratophakia have been in aphakic children.

Dr Irene H. Maumenee. First of all, let me thank Doctor Robb who certainly and indeed did not get the manuscript in time and he certainly has been very patient with me sending him sections. Thanks to Fax they go there every 3 days with something new added on.

As regards the question of astigmatism and refractive errors, I would like to stress that there were a large number of patients who had very high myopia, −5.00 to −20.00 D. You can observe significant axial myopia in colobomatous eyes. You should certainly not assume that every patient who has microcornea and coloboma will turn out to be hypermetropic. Thus, you can find the opposite and very long globes have been measured using scanning methods. Astigmatism is obviously part of this disease. In no case have we used epikeratophakia, the overall problems are usually overwhelming and it has not occurred to me to do so.

Contact lenses—I don't see any reason why they shouldn't be tried and certainly one can fit very small corneas as is often necessary and successfully done in patients with congenital cataracts. I do not remember a patient in this group, who is wearing contact lenses but I do not see any reason why that should not be done.

As regards Doctor Parks' question—we have one patient who developed a retinal detachment in both eyes, both eyes being inoperable and one patient who got a retinal detachment in one. We certainly have seen a number of serous

detachments of the macula. I have to get back to the patient data to see in how many patients it actually has occurred. But that is a well-known and definite complication of this entity. Retinal detachments usually occur because of tears at the edge of the coloboma, they are notoriously hard to fix.

Certainly the most difficult factors in data analysis is to correct for are artifacts created by bias of ascertainment. We are proud to be a referral center, which, however, leads to unmeasurable errors of ascertainment. On the other hand many problems are probably overlooked. For example, we recently saw a patient who had been followed in a major US eye clinic in the South. He was diagnosed as having bilateral glaucoma, his follow-up occurred in a major center in New York, where his presumed glaucoma was treated medically over many years. Argon laser trabeculoplasties were also performed. He was examined at the Glaucoma Center at The Wilmer Institute and his glaucoma was judged cured. He was taken off pilocaropine, at which time his problems with night vision disappeared. Because of the diagnosis of probable retinal dystrophy given his complaints of night vision problems and the diagnosis of retinitis pigmentosa in his maternal uncle he was seen at the retinitis pigmentosa center at the Wilmer Institute. His ERG was essentially normal. At that point he was referred to me. The patient had bilaterally optic nerve head colobomas in a morning glory fashion. He had had bilateral serous detachments of the macula leading to pigment migration in the macular area. The primary problem was colobomatous malformations of the optic nerve head leading as far as argon laser trabeculoplasties. In addition, he reported long-standing renal insufficiency of unknown etiology. He proved to have bilaterally hypoplastic kidneys which are probably part of his malformation syndrome. This correlation had not been made. Thus there is likely general underascertainment of extraocular complications, specifically renal complications. They are probably present in a much higher proportion of patients than we are aware of, given the fact that if asymptomatic they are not being looked for, or even that the association is not being made. In practice there are probably more patients who have associations than is apparent and we probably get more referrals of complicated patients, making the prevalence of a smaller proportion of syndromal patients likely than our figures indicate, but larger than generally assumed.